## REMARKS

Applicants have received and reviewed an Office Action dated June 15, 2007. By way of response, Applicants have canceled claim 22 without prejudice. Claims 1-21 are pending.

For the reasons given below, Applicants submit that the amended claims are in condition for allowance and notification to that effect is earnestly solicited.

### Claim Rejections – 35 U.S.C. § 103(a)

The Examiner rejected claims 1-7 and 22 under 35 U.S.C. § 103(a) as obvious over Schumacher et al., WO 99/01450. The Examiner rejected claims 1-20 under 35 U.S.C. § 103(a) as obvious over Schumacher et al. in view of Villani et al., WO 85/03707. Applicants respectfully traverse these rejections.

Applicants respectfully submit that the cited references do not in fact disclose substantially pure (>99.5%) desloratadine wherein the impurity observed by HPLC at a relative retention time of about 0.85 to 0.99 is eliminated. Nor do the cited references provide any motivation to employ Applicants' method in order to result in the elimination of this impurity. The present application discloses that an impurity at relative retention time of about 0.85 to 0.99 is formed by the prior art process (at least at page 10, lines 22-25, referring to the publications WO 8503707 and WO 9901450). In addition, HPLC of the commercial and marketed composition Neoclarityn shows impurity at a relative retention time of 0.91 (present application at least at paragraph bridging pages 11-12). Thus, while the cited references teach desloratidine purities of greater than 99.5%, they do not teach a method or composition that provides an absence of the impurity observed by HPLC at a relative retention time of about 0.85 to 0.99.

In support of this assertion, Applicants submit laboratory notebook pages as Exhibit A, which is an outline of the synthesis and purification of desloratidine prepared according to WO 99/01450. An HPLC analysis of the crude product made according to WO 99/01450 is submitted at Exhibit B; an analysis of this product as purified according to the present invention submitted at Exhibit C. In the HPLC analyses, both the crude desloratidine and the purified deloratidine have a peak corresponding to an impurity that is detectible at a retention time of 0.85 to 0.99 relative to the peak corresponding to the desloratidine product. While purification

results in a total impurity of slightly less than 0.5%, 0.375% of the total impurity corresponds to the impurity having a relative retention time of 0.85 to 0.99. In sharp contrast, Applicants method results in a complete elimination of detectible amounts of the impurity that is detectible at a retention time of 0.85 to 0.99 relative to the peak corresponding to the desloratidine product.

Applicants have eliminated a substantial byproduct that arises as a result of all methodologies known prior to that of the claimed invention, including those of the cited references. This result is unexpected and surprising, as one of ordinary skill in the prior art would not expect Applicants' method to result in the absence of the compound whose HPLC trace reveals its presence in every other method of synthesis and purification. This unexpected result is evidence of nonobviousness of the methods employed by Applicants.

The MPEP states at section 716.02(a) that absence of a property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness. *Ex parte Mead Johnson & Co.* 227 USPQ 78 (Bd. Pat. App. & Inter. 1985). Such a legal conclusion must necessarily extend to absence of a chemical entity which a claimed invention would have been expected to possess based on the teachings of the prior art, because presence or absence thereof affects the properties of the product. Such must also be the case even where the chemical composition has the same general usefulness as a prior art composition, because chemical impurities present in minor amounts do not necessarily destroy the usefulness of the major component(s). Instead, impurities may have effects that are not recognized until it is possible to provide a composition not having that impurity. For example, the impurity may be responsible for one or more side effects where the chemical composition is a drug composition. An impurity may also effect the degree of crystallinity of the composition.

Additionally, Applicants respectfully submit that whether a given chemical compound has the same usefulness as a prior art compound is only one consideration in establishing obviousness. Other factors which must be given weight in determining whether the subject matter as a whole would have been obvious include whether the prior art suggests substantially pure desloratadine with HPLC purity greater than 99.5% free of impurity at a relative retention time of about 0.85 to 0.99. Applicants respectfully submit that the presently claimed compounds and methods are not obvious by this standard. None of the cited references suggest a method by

which such a product can be made; and there is nothing in the cited references to motivate one of skill in the art to arrive at Applicants' composition or method.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the presently claimed compounds and processes are neither taught nor suggested by the references cited in the office action, and withdrawal of this rejection is respectfully requested.

**Claim Rejections – 35 U.S.C. § 112, first paragraph**

Claim 22 was rejected under 35 U.S.C. § 112, first paragraph, as including new matter. Applicants respectfully traverse this rejection.

Without acquiescing to the rejection, and solely to further prosecution of the application, Applicants have canceled claim 22 without prejudice.

Accordingly, Applicants respectfully submit that the claims fully comply 35 U.S.C. § 112, first paragraph and withdrawal of this rejection is respectfully requested.

**Summary**

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please charge any additional fees or credit any overpayment to Merchant & Gould P.C., Deposit Account No. 13-2725.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: 11 Oct '07

Mark T. Skoog
Reg. No. 40,178

MTS:kf

# EXHIBIT A

# USSN 10/510,619

EXPT NO. : 17

SUN PHARMACEUTICAL INDUSTRIES LTD.

**SUN PHARMA ADVANCED RESEARCH CENTRE**
**ORGANIC SYNTHESIS**

# PROCESS DATA SHEET

| | | | |
|---|---|---|---|
| PROJECT : | SUN-8024 | CHEMIST : | Bhuva, Vimal. R. |
| STAGE : | — | GROUP LEADER : | Dr. C.T. Rao. |
| BATCH : | 8024/485/17 | DATE : | 08/04/02. |

OBJECTIVE / AIM : To prepare Desloratadine as per Pat. WO 99/01450 (ex.-2).

EQUIPMENT : 500 ml reactn. flask, condenser, Otts etc.

SAFETY MEASURE :

| No. | Chemicals | M. Wt. | Qty. | Wt / ml | Moles | Mole Ratio | Grade / Source | Purity / water % |
|---|---|---|---|---|---|---|---|---|
| 1 | Loratadine | 382.84 | 45.0 g | — | 0.117 | 1.0 | Cadila | |
| 2 | KOH pellets | 56.1 | 40.5 g | | 0.721 | 6.14 | S.d.fine | |
| 3 | Ethanol | — | 180 ml | — | — | 4 V/W | comm | |
| 4 | MIBK | — | 360 ml | — | — | 8 V/W | comm | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

PRODUCT DETAILS : NAME :

TR. NO. 02/K/60 DATE 09/04/02 AR NO. SO2-1891 DATE 10/04/02

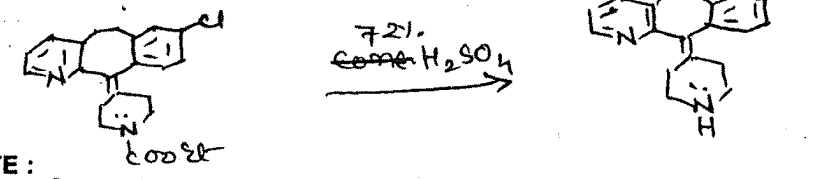
| | | | | | |
|---|---|---|---|---|---|
| DRIED AT ..... | °C (under Vac./Air) | | | CRUDE YIELD | PURIFIED YIELD |
| DISTILIED I) | °C / | mm / Hg | | g | 28.0 gm |
| FRACTIONS : II) | °C / | mm / Hg | | % w/w | — % w/w |
| | °C | mm / Hg | | % Moist. | — % Moist. |
| M.P. : °C | HPLC / GC / TITR | | | % Th. | 76.89% Th. |

OTHER ANALYSIS : HPLC : Crude → Method: I II Pure → I II
Major imp : 0.18% 0.59% major imp : 0.14% 0.37%
Purity : 99.68% 99.33% Purity : 99.82% 99.52%

CONCLUSION / REMARKS This exp. was performed to check the validation of process.

Experimented by : Bhuva
Date : 10/04/02

**CHEMICAL EQUATION :**




**DATE :** 23.09.02

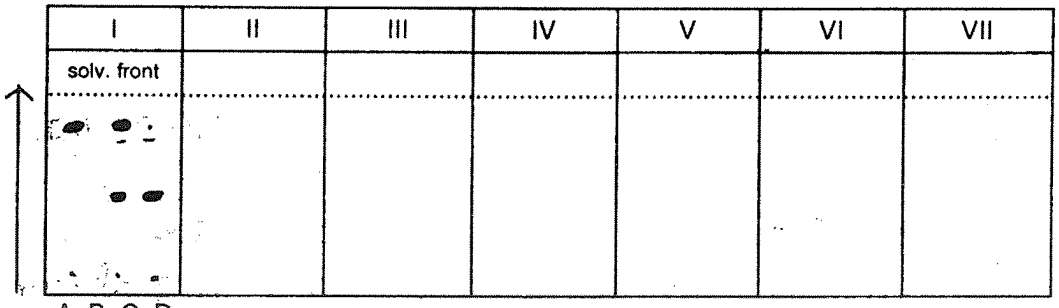
| Step No. | QTY. | OPERATION | Time From | Time To | OBSERVATION & REMARKS |
|---|---|---|---|---|---|
| 1. | | charged to an rb flask. | | | |
| | 19.5 g | Loratadine | 3:45 | 4:00 | |
| 2. | | In a seperate flask | | | |
| | | mixed | | | |
| | 10.5ml | d.m. water & | | | |
| | 16ml | conc. $H_2SO_4$ & at 0°c | 4:00 | 4:15 | clear soln, |
| 3. | | charged above solution of | | | |
| | | step-2 to loratadine | 4:15 | 4:20 | no clear soln. |
| 4. | | Reaction temperature | | | |
| | | was raised to 115°c | 4:20 | 4:30 | clear soln. |
| 5. | | Refluxing at 115°c was | | | |
| 24.09.02 | | continued | 4:30 | 10:30 | clear soln. |
| 6. | | TLC was checked TLC-I | 9:30 | 9:45 | Reaction over |
| 7. | | charged | | | |
| | 100ml | methanol to reaction mix. | | | |
| | | under stirring. | 9:40 | 9:50 | clear soln. |
| 8 | | Reaction mix. was cooled | | | |
| | | to 0°c | 9:50 | 10:00 | clear soln |
| 9. | | stirred at 0°c | 10:00 | 1:00 | clear soln. |
| 10. | | Stirring was continued | 1:00 | 5:30 | clear soln |
| 11. | | Stirring was stopped & | | | |
| | | reaction mix. was | | | |
| | | discarded | | | |

Experimented by : Rupal

Date : 23.09.02

# IN PROCESS CONTROL ANALYTICAL PARAMETERS

THIN LAYER CHROMATOGRAPHY (TLC MONITORING)




| SPOT DESCRIPTION | Rf value |
|---|---|
| A → reaction mix. | |
| B → co-spot | |
| C → Loratadine in EtOAc | |
| D → | |

TLC PLATE DESCRIPTION :

- reaction mix. wat was taken out, quenched with water, basified to pH = 14 & extracted in EtOAc

**SOLVENT SYSTEM : (TLC)** MDC : MeOH : $NH_3$ (8 : 1.8 : 0.2)

**DETECTION** : UV Long / Short ✓
$I_2$ Vapour /

**ADSORBENT** : Silica gel / Alumina ✓

*SOLUBILITY INFORMATION :*

*SOLVENT RECOVERY INFORMATION :*

Experimented by : Rupal

Date : 24.09.02

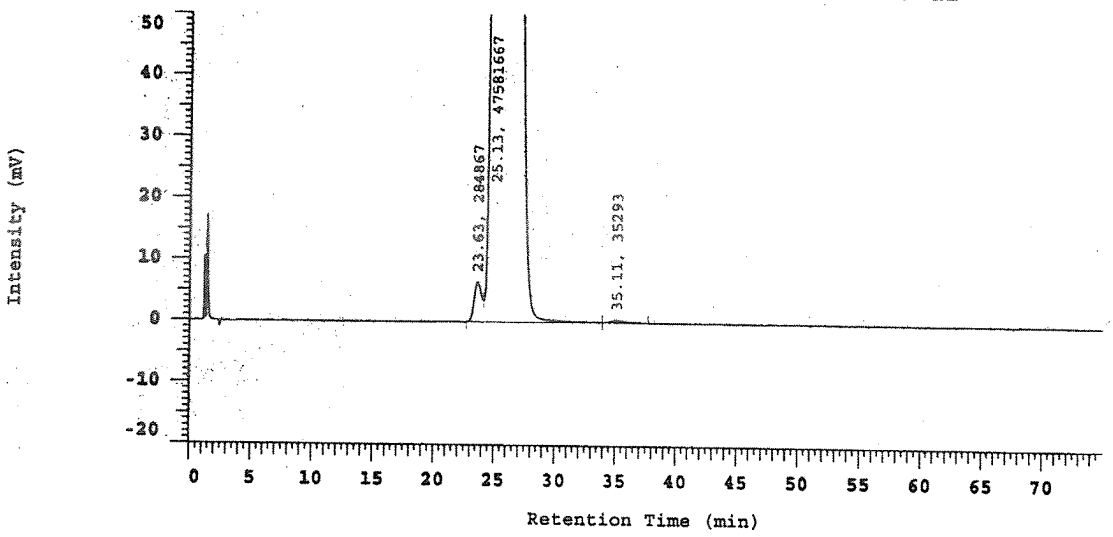
# EXHIBIT B

# USSN 10/510,619

# ADD SPARC BARODA

Analyzed: 04/09/02 11:57 PM
Processed: 04/10/02 09:42 AM
Data Path: E:\backup C\Win32App\HSM\alp\DATA\1638\
Processing Method: 8024
System(acquisition): HPLC 19
Sample Name: 8024/M II/485/17 CRUDE

Series:1638
Vial Number: 8
Vial Type: UNK
Volume: 20.0 ul




| No. | RT | Area | Area % |
|---|---|---|---|
| 1 | 23.63 | 284867 | 0.595 |
| 2 | 25.13 | 47581667 | 99.332 |
| 3 | 35.11 | 35293 | 0.074 |
| | | 47901827 | 100.000 |

Peak rejection level: 0

HPLC of crude desloratadine (Method II)
prepared as per Patent No WO 99/01450

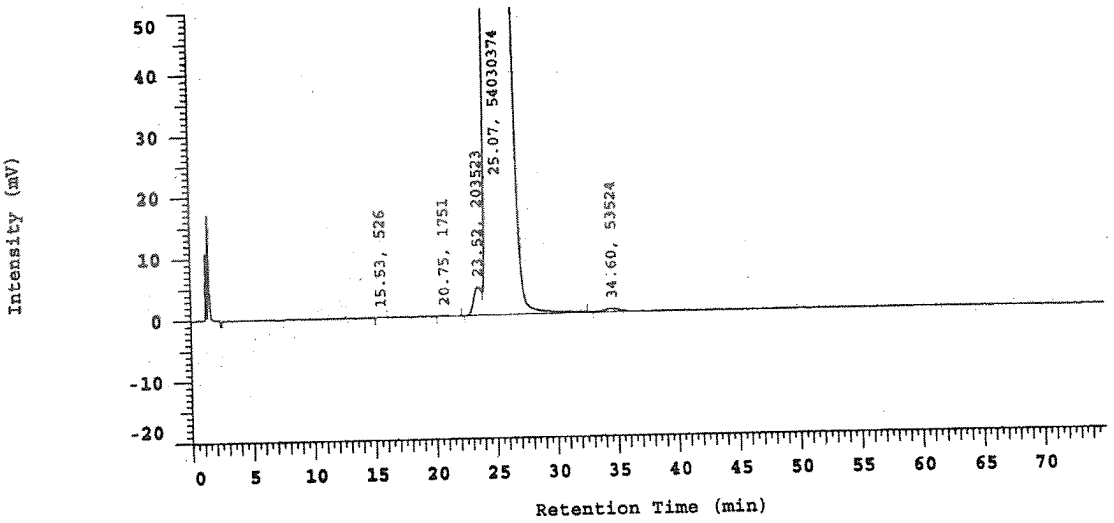
# EXHIBIT C

# USSN 10/510,619

# ADD SPARC BARODA

Analyzed: 04/09/02 08:07 PM
Processed: 04/10/02 09:39 AM
Data Path: E:\backup C\Win32App\HSM\alp\DATA\1638\
Processing Method: 8024
System(acquisition): HPLC 19
Sample Name: 8024/M II/485/17 PURE

Series:1638
Vial Number: 5
Vial Type: UNK
Volume: 20.0 ul




| No. | RT | Area | Area % |
|---|---|---|---|
| 1 | 15.53 | 526 | 9.696E-04 |
| 2 | 20.75 | 1751 | 0.003 |
| 3 | 23.52 | 203523 | 0.375 |
| 4 | 25.07 | 54030374 | 99.522 |
| 5 | 34.60 | 53524 | 0.099 |
| | | 54289698 | 100.000 |

Peak rejection level: 0

HPLC of purified desloratadine (Method II)
prepared as per Patent No WO 99/01450